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(54) Title: STABLE BIOCIDAL COMPOSITIONS

(57) Abstract: A stable veterinary composition suitable for pour on or oral use as a anthelmintic where a benzimidazole is carried in lactic acid (optionally with a co-solvent such as NMP).

"STABLE BIOCIDAL COMPOSITIONS"

THE CURRENT INVENTION

The present invention relates to veterinary benzimidazole formulations and preferably to pour-on formulations of physically stable clear liquid formulations of benzimidazole compounds and related uses.

SUMMARY OF THE INVENTION

A particular (but not only) area of interest in stable veterinary formulations of a benzimidazole are with those formulations of benzimidazole biocides useful in controlling helminths (including nematodes, cestodes, trematodes, and protozoa) in mammals. Different modes of administration of such formulations include the oral, injectable or pour-on (transdermal) routes. Stability is desirable so that a formulation can be stored and the formulation used or reused at a later date without degradation of the active(s) or significant physical changes to the formulations which will lead to dosage variations.

Benzimidazoles are poorly soluble in water and oils.

For this reason both commercial pour-on and oral formulations to date exist as suspensions with the benzimidazole present as fine particles.

In PCT/NZ95/00023 (published as WO 95/23590 on 8 September 1995) Bomac Laboratories Limited discloses a multi phase pour-on benzimidazole composition where the benzimidazole (or pro-drug thereof) is dissolved in, suspended on and/or emulsified by a transdermal vehicle and such mixture of the benzimidazole (or the pro-drug) with the transdermal vehicle is in turn carried in a liquid carrier which includes a non-ionic emulsifier, an oil which solubilises the non-ionic emulsifier, water or other suitable diluent, and a deflocculation agent.

Suspensions have a number of problems, principally settling of particles over time, difficulties in resuspending which requires regular and vigorous shaking and the particles can be abrasive to drench guns. Additionally when delivered by either the pour-on or oral route many of these particles are not absorbed but remain on the skin or within the gut where they are less able or available to exert their anthelmintic action. With benzimidazoles the smaller the particle size (ie; micronised) the more effective the

benzimidazole becomes as an anthelmintic.

A "solution" of a benzimidazole, such as described in the present invention, overcomes many of these problems.

As used herein the term "anthelmintic" and derivatives thereof shall encompass, where the context allows any one or more of a nematocidal, trematocidal and cestocidal active compounds.

As used herein the term "benzimidazole" or "benzimidazoles" refers to anthelmintically effective benzimidazole(s) and includes pro-drugs thereof that can be solubilised in lactic acid yet provide, upon transdermal movement, a requisite benzimidazole anthelmintic effect upon hydrolysis, reduction or cyclization.

As used herein the term "stable" means at least 3 months (preferably at least 18 months) chemical stability (eg; within plus or minus 10% $^{w}/_{w}$ of its stated composition) of the active ingredients when stored at 25°C or below and at ambient humidity and of reasonable physical stability such that the composition is substantially homogeneous (despite any option particulate inclusion(s)) and/or can readily be agitated to such condition.

As used herein "veterinary" refers to mammals other than humans.

When used in conjunction with a combination of a benzimidazole and lactic acid the term "solubility" covers everything from true solubility to any other physical or chemical state that exists between the benzimidazole and the lactic acid which nonetheless gives the appearance of a stable clear and substantially homogenous looking liquid phase. This is because whilst it is believed there is actual solubility it may subsequently be found that some or all of the benzimidazole may be present in the lactic acid other than as a true solute (ie; may be present as fine particles or micelles).

As referred to herein the term "pourable" or "flowable" in respect of a fluid or liquid covers viscosities ranging from a free flowing liquid to a gel or paste consistency that is able to be expelled by syringe, drench or paste gun. The term "pourable" is irrespective of whether it is to be used as a pour on or otherwise.

We have theorised that an organic acid such as lactic is not contra indicated as a liquid vehicle for a biocidal or other benzimidazole to be given by the pour-on route or to be given orally. Even with the pH of such organic acids little in the way of localised

skin damage is expected owing to the short duration of such acid presence on the skin whilst the benzimidazole passes through the skin and of course orally the acidity is far below that of gastric fluids and there is also dilution within ruminal fluid in ruminants.

Our experimentation however has shown the inappropriateness of a large number of the organic acids as such a liquid vehicle. Included in such organic acids that are not useful in delivering a benzimidazole are dobanic acid, citric acid, acetic acid and formic acid. These have the following deficiencies with respect to benzimidazoles (BZ).

- dobanic acid - will solubilise BZs but no longer term physical stability (i.e. BZ falls out).
- citric acid - doesn't effectively solubilise BZs.
- acetic acid - will solubilise Bzs but no longer term physical stability.
- formic acid - will solubilise Bzs but no longer term physical stability.

We have discovered however that lactic acid (preferably substantially free of impurities) does dissolve benzimidazoles and provides good longer term homogeneity (at least in appearance and physical spread of the benzimidazole therein) as well as good chemical stability. All this for an acceptable cost. We have also found such a lactic acid carried benzimidazole remains effective as both an anthelmintic oral formulation or inclusion thereof an formulation or inclusion thereof.

We have also shown that a benzimidazole carried in lactic acid is effective as a pour-on and believe it is not contraindicated as an oral delivery composition for mammals. It is envisaged that the present invention will use either a benzimidazole(s) alone, or in combination with other anthelmintic families to broaden the spectrum of activity. For example, a benzimidazole flukacide such as triclabendazole in combination with another anthelmintic such as levamisole or a macro cyclic lactone.

The present invention is directed to **a (**preferably **pourable or flowable) stable veterinary composition** (eg; for oral or pour-on use) where a benzimidazole (as previously defined) is carried in lactic acid.

Preferably a co-solvent is present.

Preferably said co-solvent is n-methyl-2-pyrrolidone.

Preferably said benzimidazole is selected from albendazole, oxfendazole, fenbendazole and triclabendazole.

Preferably up to 4% $^{w}/_{v}$ of albendazole or oxfendazole or triclabendazole is present.

In some forms triclabendazole or other benzimidazole comprises more than 4% $^{w}/_{v}$ of the composition and preferably a co-solvent is present. There is a need for more concentrated formulations up to 10% $^{w}/_{v}$ for larger animals such as cattle to reduce the volume of the product to be delivered.

In another aspect the invention consists in **a pourable or flowable stable veterinary composition** comprising lactic acid and the benzimidazole carried thercin.

Preferably a co-solvent (such as NMP (n-methyl-2-pyrrolidone) may be present).

In another aspect the invention is **a stable topical or pour-on veterinary composition** where at least one benzimidazole is carried in lactic acid, the benzimidazole(s) present in the lactic acid being less than 10% $^{w}/_{v}$.

In a further aspect the present invention consists in **a pourable or flowable stable topical or pour-on veterinary composition** where a benzimidazole is carried in lactic acid.

Preferably a co-solvent (such as NMP (n-methyl-2-pyrrolidone) may be present.

In a further aspect the present invention consists in **a benzimidazole containing veterinary composition of at least two liquid phases** where at least one stable phase is that of lactic acid (optionally with at least one co-solvent e.g. NMP) which carries at least one benzimidazole.

Preferably n-methyl-2-pyrrolidone is present as the or a said co-solvent.

In another aspect the invention is **a composition** of any of the kinds substantially as herein described with reference to any of the examples.

In a further aspect the invention is **a method of treating a ruminant mammal** for nematodes, trematodes and/or cestodes which comprises orally administering to any such mammal an anthelmintically effective quantity of a composition of the present invention.

In another aspect the invention is **a method of treating a ruminant mammal** for nematodes, trematodes and/or cestodes which comprises pour-on administering to any such mammal an anthelmintically effective quantity of a composition of the present invention.

In yet another aspect the invention is, **as a component in an anthelmintic composition**, a lactic acid containing phase in which at least one benzimidazole is present.

We have determined with lactic acid:

- The preferred form of lactic acid is 80% Food Grade. Impurities in other grades tends to lead to less stability.
- Many organic acids (such as dobanic, citric, acetic and formic acids) are unsatisfactory for differing reasons. In these cases the Benzimidazole was initially solubilised but eventually precipitated on standing. Citric Acid was impractical given that it was trialed in solid form.
- Mineral chelates and salts significantly reduce formulation stability.
- Benzimidazole formulations in lactic acid remain physically stable for up to 5 years.
- Closantel and Closantel Sodium are insoluble in lactic acid.
- Benzimidazole/lactic acid formulations can be administered to mammals (eg; cattle) by the pour-on route and are effective.
- Lactic acid has been loaded with the following;
  - Albendazole and Oxfendazole - up to 4% w/v
  - Triclabendazole - up to 10% w/v
  - Levamisole HCl - up to at least 6% w/v
  - Praziquantel - up to at least 4% w/v.

  The lower the active loading the more like the formulation to remain stable.
- Adding a small quantity of a solvent such as NMP greatly enhances the Benzimidazoles solubility in Lactic Acid.
- These formulations are unstable in the presence of water. Although they show a short-term tolerance of up to 30% water contamination, they will eventually precipitated active. The precipitate is very fine with a particle size under 2 microns.
- Water or aqueous phase dilution prior to use is feasible.

Stability:

The following formulations have been prepared for an explanatory chemical stability study.

- **Example 1:**

1.45% w/v Oxfendazole and 0.50% w/v Triclabendazole

- **Example 2:**

3.8% w/v Levamisole and 0.50% w/v Triclabendazole.

Both formulations have been fully tested and have shown stability as hereinbefore described.

- **Table 1:**

Criteria	Example 1	Example 2
Appearance	Clear slightly amber liquid	Clear colourless liquid
Specific Gravity @20°C	1.186	1.209
% Oxfendazole	1.44%	-----
% Levamisole	-------	3.84%
% Triclabendazole	0.50%	0.50%

EXAMPLE 3

Benzimidazole Active in Lactic Acid

Carnola Oil	40.00 % w/v
Teric 380	5.00 % w/v
Abamectin	0.10% w/v
Promyristyl Propionate	3.00 % w/v
Oxfendazole	4.00 % w/v
Levamisole HC1	3.75% w/v
Lactic Acid	To volume

Formulated Order:

- Mix 1 - Dissolve Abamectin in warmed emollient Ester (Promyristyl Propionate) then mix into Oil. Mix in Teric 380.
- Mix 2 - To Lactic acid dissolve Oxfendazole and Levamisole (slight heat required).

- Mix 3 - Combine mixes 1 and 2 with high shear agitation

Example 3 Findings:

- These soluble forms of benzimidazoles are dermally absorbed as pour-on formulations. May include a thickener.

EXAMPLE 4

Benzimidazole Active in Lactic Acid

Carnola Oil	40.00 % w/v
Teric 380	5.00 % w/v
Abamectin	0.10% w/v
Promyristyl Propionate	3.00 % w/v
Triclabendazole	0.50% w/v
Oxfendazole	4.00% w/v
Levamisole HC1	3.75% w/v
Lactic Acid	To Volume

Formulated Order:

- Mix 1 - Dissolve Abamectin in warmed emollient Ester (Promyristyl Propionate) then mix into Oil. Mix in Teric 380.
- Mix 2 - To Lactic acid dissolve Oxfendazole or Levamisole and Triclabendazole (slight heat required).
- Mix 3 - Combine mixes 1 and 2 with high shear agitation

Example 4 Findings:

- As above, likely to have application as a pour-on formulation. May include a thickener.

Examples 5 & 6

Formulation	Example 5	Example 6
Albendazole	2.5% w/v	-
Oxfendazole	-	3.75% w/b
Lactic Acid, Food Grade	To Volume	To Volume

Method of Manufacture: Dissolve Benzimidazole in Lactic Acid. The Oxfendazole formulation required warming to 30°C.

Examples 7 & 8:

It was found that using a co-solvent such as N-methyl-2-pyrrolidone (NMP) greatly increased the potential loading of a Benzimidazole. In the case of Triclabendazole the

potential loading was increased from 1.0% (Example 7) with only lactic acid to 10% (Example 8) using a co-solvent.

Formulation	Example 7	Example 8
Triclabendazole	1.0% w/v	10.0% w/v
N-methyl-2-pyrrolidone	-	20.0% w/v
Lactic acid, Food Grade	To Volume	To Volume

Method of Manufacture: Dissolve Benzimidazole in Lactic Acid and NMP blend. No heating required.

ANIMAL STUDIES

Faecal Egg Counts (FEC's) Dosages by Reference to Anthelmintic Actives

- **Trial NUA01 : Sheep Oral**

Group 1 - Untreated Control

Group 2 - Albendazole (Lactic Acid) - Dose 5 mg/kg

Group 3 - Albendazole (Commercial Suspension) - Dose 5 mg/kg

The Group 2 study was with 2.5% $^{w}/_{v}$ Albendazole

The Group 3 study was with 1.9% $^{w}/_{v}$ Albendazole (VALBAZEN™).

- **Trial NU001 : Cattle Pour-On**

Group 1 - Untreated Control

Group 2 - Oxfendazole (Lactic Acid) - Dose 15 mg/kg

Group 3 - Oxfendazole (Commercial Pour-On Suspension) - Dose 15 mg/kg

Group 4 - Triclabendazole - Dose 10 mg/kg

The Group 4 study was with 10% $^{w}/_{v}$ Triclabendazole as in Example 8.

The Group 3 study was with 7.5% $^{w}/_{v}$ Oxfendazole (BOMATAC™)

The Group 2 study was with 3.75% $^{w}/_{v}$ Oxfendazole.

SHEEP TRIAL

Nufarm NUA01 Data

ID	Group	FEC Pre Trial	Weight Day 0	Day 1
2	1	1400	24.0	800
10	1	880	21.0	560
13	1	920	20.0	680
1	2	520	17.0	40
4	2	560	23.0	160
8	2	1160	21.5	320
11	2	1520	20.0	120
3	3	640	22.5	400
5	3	1040	25.0	160
9	3	1680	20.5	200
6	cull	0	-	-
7	cull	40	-	-
Entered		MAC	MAC	MAC
Date		12-Jul-00	19-Jul-00	19-Jul-00
Verified				
Date				

Nufarm NUA01 Group Means

Group	Treatment	FEC Pre Trial	Weight Day 0	Day 1
1	Control	108.7	21.7	680.0
2	Nufarm ABZ	940.0	20.4	160.0
3	Valbazen	1120.0	22.7	253.3

Nufarm NUA01 Efficacies

Group	Treatment	Day 1
2	Nufarm ABZ	76.5%
3	Valbazen	62.7%

Notes: Nufarm ABZ = Albendazole 25 mg/mL

Valbazen = Albendazole 19 mg/mL

CATTLE TRIAL

Nufarm NU001 Data

ID	Group	Treatment	FEC Pre Trial	Weight Day 0	FEC Day 1
3358	1	Control	1200	178	1120
9234	1	Control	2080	180	1360
9255	1	Control	960	186	1680
3353	2	OXFZ	1000	184	160
3354	2	OXFZ	1200	186	1680
9488	2	OXFZ	1480	186	440
9081	3	Bomatak	1120	180	920
9118	3	Bomatak	1080	166	880
9489	3	Bomatak	1480	176	800
3352	4	TLBZ	1800	176	
9233	4	TLBZ	920	178	
9300	4	TLBZ	1120	182	
		Entered	JC	MAC	MAC
		Date	13-Jul-00	19-Jul-00	19-Jul-00
		Verified			
		Date			

Nufarm NU001 Group Means

Group	Treatment	FEC Pre Trial	Weight Day 0	FEC Day 1
1	Control	1413.3	181.3	1386.7
2	IXFZ	1226.7	185.3	160.0
3	Bomatak	1226.7	174.0	800.0
4	TLBZ	1280.0	178.7	

Nufarm NU001 Efficacies

Group	Treatment	FEC Day 1
2	OXFZ	43.2%
3	Bomatak	42.3%

Note: TLBZ = Triclabendazole

CLAIMS:

1. **A stable veterinary composition** where a benzimidazole (as hereinbefore defined) is carried in lactic acid.

2. A composition as claimed in claim1 which is an oral anthelmintic composition for ruminant mammals.

3. A composition as claimed in claim 1 which is a pour-on anthelmintic composition effective for ruminant mammals.

4. A composition as claimed in any one of the preceding claims wherein a co-solvent is present.

5. A composition as claimed in claim 4 wherein said co-solvent is n-methyl-2-pyrrolidone.

6. A composition as claimed in any one of the preceding claims wherein said benzimidazole is selected from albendazole, oxfendazole, fenbendazole and triclabendazole.

7. A composition as claimed in any one of the preceding claims having up 4% w.v of albendazole or oxfendazole.

8. A composition as claimed in any one of claims 1 to 6 having up to 4% w/v triclabendazole.

9. A composition as claimed in any one of claims 1 to 6 wherein triclabendazole comprises more than 4% w/v of the composition and a co-solvent is present.

10. A composition of any one of the preceding claims which is pourable or flowable.

11. **A stable topical or pour-on veterinary composition** where at least one benzimidazole is carried in lactic acid, the benzimidazole(s) present in the lactic acid being less than 10% w/v.

12. A composition as claimed in claim 11 wherein n-methyl-2-pyrrolidone is present as a co-solvent.

13. **A benzimidazole containing veterinary composition of at least two liquid phases** where at least one liquid phase is stable phase of lactic acid (optionally with at least one co-solvent) and at least one benzimidazole.

14. A composition as claimed in claim 13 wherein n-methyl-2-pyrrolidone is present as the or a said co-solvent

15. A composition of any of the kinds substantially as hereinbefore described with reference to any of the examples.

16. **A method of treating a ruminant mammal** for nematodes, trematodes and/or cestodes which comprises orally administering to any such mammal an anthelmintically effective quantity of a composition as claimed in any one of the preceding claims.

17. A method of treating a ruminant mammal for nematodes, trematodes and/or cestodes which comprises pour-on administering to any such mammal an anthelmintically effective quantity of a composition as claimed in any one of claims 1 to 15.

18. **As a component in an anthelmintic composition,** a lactic acid containing phase in which at least one benzimidazole is present.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/NZ00/00130

A. CLASSIFICATION OF SUBJECT MATTER

Int. Cl. [7]: A01N 43/52, 25/02, A61K 31/4184

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IC[7]:A01N 43/52, 25/02, A61K 31/4184
IC[6]: A61K 31/415

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
WPAT: (lactic acid AND IC marks as above); [(albendazol+ OR oxfendazol+ OR fenbendazol+ OR triclabendazol+) AND lactic+]; (benzimidazol+ AND lactic+)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Derwent Abstract Accession No. 28084C/16, Class B02, JP 55-031,028 (DAIICHI SEIYAKU KK) 5 March 1980 - see abstract	1-18
X	Derwent Abstract Accession No. 21453D/13, Class A96 B02 C02, BE 885,178 (ELI LILLY & CO) 11 March 1981 - see abstract	1-18
X	Derwent Abstract Accession No. 26659 K/11, Class B02 C02, JP 58-021615, (FUJISAWA PHARM KK) 8 February 1983 - see abstract	1-18

[X] Further documents are listed in the continuation of Box C [X] See patent family annex

* Special categories of cited documents:

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"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
19 October 2000	20 NOV 2000
Name and mailing address of the ISA/AU	Authorized officer
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INTERNATIONAL SEARCH REPORT

International application No.
PCT/NZ00/00130

C (Continuation). **DOCUMENTS CONSIDERED TO BE RELEVANT**

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5177110 A (Oechslein, W. *et al* .), 5 January 1993 - see whole document	1-18
A	US 5104873 A (Nowak, E. and Foster, J.C.), 14 April 1992 - see whole document	1-18

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/NZ00/00130

This Annex lists the known "A" publication level patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent Document Cited in Search Report		Patent Family Member					
US	5104873	AU	66864/90	EP	432092	GB	8926486
		NZ	236184	ZA	9009366		

END OF ANNEX